Endothelin receptor antagonist CPU0213 suppresses ventricular fibrillation in L-thyroxin induced cardiomyopathy

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Abstract:
Arrhythmias correlate with disorders of either K⁺ channels in sarcolemma or calcium modulating system in sarcoplasmic reticulum which handles Ca²⁺ intracellularly. We hypothesized that an activated endothelin (ET) signaling pathway, which may be associated with an alteration of K⁺ channels and Ca²⁺ uptake activity in the myocardium, participated in the exaggerated ventricular fibrillation (VF) incidence in cardiomyopathy (CM) induced by L-thyroxin. We intended to test if a dual endothelin receptor antagonist CPU0213 is effective to suppress VF correlating with a reversal of abnormalities in expression of the ion channels in sarcolemma and sarcoplasmic reticulum. The CM was induced by L-thyroxin administration for 10 days, and the altered expression of ion channels and the ET system was examined and the susceptibility to VF was evaluated by 10-min ischemia followed by reperfusion (I/R). Rats were treated with either propranolol or CPU0213 from day 6–10 of L-thyroxin medication. An increased VF incidence on I/R episode in the CM was found relative to control. An elevated myocardial ET-1 and preproET-1 expression were associated with abnormal mRNA level of sarcoplasmic/endoplasmic reticulum Ca²⁺-ATPase 2a (SERCA2a), phospholamban (PLB), and ERG, MinK, and Kv4.2 in sarcolemma. Propranolol and CPU0213 were equally effective in reversing the alterations of gene phenotype and exaggerated VF in CM hearts. In conclusion, an activated ET receptor signaling plays a role in the progression of augmented VF in association with abnormal expression of ion channels in both sarcolemma and sarcoplasmic reticulum in the CM.

Key words:
CPU0213, endothelin receptor antagonist, K⁺ channels, ventricular fibrillation, L-thyroxin, ET-ROS pathway, SERCA2a